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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/667,328	09/21/2000	Gary W. Pace	121-112	8438

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EXAMINER	
GOLLAMUDI, SHARMILA S	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 10/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/667,328	PACE ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,24,39-42 and 44-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-24, 39-42, and 44-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Request for Reconsideration received on July 7, 2004 is acknowledged. Claims **23-24, 39-42, and 44-54** are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 23 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

Claims 23 recite campothecin, a derivative of campothecin, paclitaxel, a derivative of paclitaxel" which is indefinite since it is unclear what this encompasses. The applicant is requested to define "derivative" of the respective drug and cite support for the definition. Applicant's specification merely recites derivative and one of ordinary skill would not be apprised of the metes and bounds of the invention.

Response to Arguments

Applicant provides a dictionary definition of the term "derivative" and argues that the term is well known in the art.

Applicant's arguments have been fully considered but they are not persuasive. The examiner is well aware of the definition of the term; however it is not the term that is being questioned, rather what the term encompasses. Numerous derivatives are known in the art with the removal or addition of moieties, the applicant has not provided the specific derivatives,

which fall within the recited "derivatives" since applicant is not entitled to every derivative present in the art and future derivatives.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of 24 is rejected under 35 U.S.C. 102(b) as being anticipated by GB 1,527,638 is maintained.

GB discloses a niclosamide suspension. The formulation contains niclosamide (particle size of 2 to 20 microns) in sesame oil, polyoxyethylene-sorbitan monooleate, and 10% n-butanol. See examples. Additionally, lecithin is utilized in the examples. The suspension is administered to an animal.

Note that the limitation "wherein upon addition of said composition..." is intended use since the claim does not require the addition of the fluid aqueous medium. Furthermore, this limitation is inherent since the oil suspension will inherently form droplets when combined with an aqueous medium and since GB teaches the administration of the formulation to an animal; GB anticipates the instant invention.

Response to Arguments

Applicant's arguments filed 7/7/04 have been fully considered but they are not persuasive.

Applicant argues that GB does not anticipate since GB only discloses only niclosamide or salts thereof, but not teach any other water-soluble biologically active agents. Applicant argues that GB does not disclose a non-aqueous suspension that self-disperses in an aqueous medium. Applicant argues that self-dispersion of an oily suspension in an aqueous medium is not inherent.

Firstly, the examiner points out that claim 24 does not recite any specific drugs and only broadly claims a "water-insoluble biologically active substance". Thus, GB anticipates the instant claim since it teaches a water-insoluble active substance, i.e. niclosamide.

Secondly, the examiner points out that that the limitation "wherein upon addition of said composition..." is intended use since the claim does not *require* the addition of the fluid aqueous medium, thus the prior art need only be *capable* of performing the said intended function. It is the examiner's position that GB's composition is inherently capable of self-dispersing and the rationale is as follows. Firstly, the instant composition and GB are not patentably distinct in structure. Therefore, if the instant claim is capable of dispersing in an aqueous medium, then the prior art also must inherently be capable of self-dispersing since both composition are the same. Secondly, it is well known that oil and water are not miscible and thus applicant's argument refuting this, is perplexing. An oil suspension will inherently disperse when contacted with an aqueous medium.

Lastly, it is pointed out that once the examiner has set forth a rationale for inherency, the burden shifts to the applicants to prove that the prior art is not capable of the intended use. Mere allegation without factual evidence cannot overcome this, thus the rejection is maintained.

The rejection of claim 24 under 35 U.S.C. 102(b) as being anticipated by Brown US 3,185,625 is maintained.

Brown discloses injectable substances. The drug particles of 1.5-35 millimicrons are encapsulated with cellulose or synthetic polymers. See column 2, lines 40-61. The powder are then suspended in oil (mineral oil) and emulsified with water. The surfactants taught are Tween 20, polyoxyethylene sorbitan monolaurate. See column 3, lines 5-16. Drugs taught are toxoid, antigens, anti-allergic agents, hormones, and therapeutics. See column, lines 54-60.

Response to Arguments

Applicant's arguments filed 7/7/04 have been fully considered but they are not persuasive.

Applicant argues that Brown teach a particle range of 1.5 to 35 milllimicrons whereas instant application' claims 0.1 to 10 micrometers.

The examiner points out that the instant claims actually claim 0.01 to 10 micrometers and not as asserted 0.1 to 10. Clearly, 1.5 to 35 millimeters, i.e. 0.0015 to 0.035 micrometers, reads on the instant range.

Again it is the examiner's position that the oil suspension is inherently capable of self-dispersing. Firstly, it is pointed out that that the limitation "wherein upon addition of said composition..." is intended use since the claim does not *require* the addition of the fluid aqueous medium, thus the prior art need only be *capable* of performing the said intended function. It is the examiner's position that Brown's composition is inherently capable of self-dispersing and the rationale is as follows. The instant composition and Brown are not patentably distinct in structure. Therefore, if the instant claim is capable of dispersing in an aqueous medium, then the

prior art must also inherently be capable of self-dispersing since both composition are the same. Furthermore, it is well known to a skilled artisan that oil and water are not miscible and thus applicant's argument refuting this is perplexing. An oil suspension will inherently disperse when contacted with an aqueous medium. Lastly, it is pointed out that once the examiner has set forth a rationale for inherency, the burden shifts to the applicants to prove that the prior art does not possess the inherent property. The mere allegation that a feature is not inherent is not factual evidence and thus the rejection is maintained.

Moreover, Brown teaches the addition of water to the oil suspension provides for an emulsion on column 3, lines 50-51. It should be noted that the "rapid agitation" is used to provide for a an even distribution of the oil particles in the water and not because it is not capable of dispersing in water, since it is an intrinsic property that water and oil are immiscible mediums.

Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejection of claim 23 under 35 U.S.C. 103(a) as being unpatentable over by Brown US 3,185,625 in view of JP 360174726 is maintained.

Brown discloses injectable substances. The drug particles of 1.5-35 millimicrons are encapsulated with cellulose or synthetic polymers. See column 2, lines 40-61. The powder are then suspended in oil (mineral oil) and emulsified with water. The surfactants taught are Tween 20, polyoxyethylene sorbitan monolaurate. See column 3, lines 5-16. Drugs taught are toxoid, antigens, anti-allergic agents, hormones, and therapeutics. See column, lines 54-60.

Brown does not specify the drug utilized.

JP teaches the use of a peptide hormone (insulin) in an injectable formula to treat diabetes.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to look to the teaching of JP and utilize insulin in Brown's formulation. One would be motivated to do so since JP teaches insulin is a hormone that treats diabetes. Therefore, one would be motivated to incorporate the drug of choice to treat the desired disease, and in this case one would be motivated to utilize insulin if one wanted to treat diabetes. Further, a skilled artisan would expect similar results since Brown teaches the suitability of hormones in the formulation.

Response to Arguments

Applicant's arguments filed 7/7/04 have been fully considered but they are not persuasive.

Applicant argues that Brown teach a particle range of 1.5 to 35 milllimicrons whereas instant application' claims 0.1 to 10 micrometers. Applicant argues that Brown does not teach a self-dispersing composition. Applicant argues that JP does not teach a self-dispersing composition. Lastly, applicant argues that Brown requires encapsulating the drug particle and instant claims do not require an additional step of encapsulation.

Firstly, as addressed in the anticipation rejection, the instant claims actually claim 0.01 to 10 micrometers and not as asserted 0.1 to 10. Clearly, 1.5 to 35 millimeters, i.e. 0.0015 to 0.035 micrometers, reads on the instant range. Also as addressed above, it is the examiner's position that Brown's composition is capable of self-dispersing in an aqueous medium for the reasons set forth above. It is the applicant's burden to proves otherwise. The applicant has not done so. Thus, since Brown teaches a composition that is capable of self-dispersing. JP does not have to teach this limitation and this argument is moot.

Secondly, it is pointed that the instant claim language does not exclude the drug particle from being encapsulated.

Therefore the rejection is maintained.

The rejection of claims 23 and 28 under 35 U.S.C. 103(a) as being unpatentable over by GB 1,527,638 in view of Hauer et al (5,342,625) or vice-versa is maintained.

GB discloses a "preconcentrate" niclosamide suspension. The formulation contains niclosamide (particle size of 2 to 20 microns) in sesame oil, polyoxyethylene-sorbiatn monooleate, and 10% n-butanol. See examples. Additionally, lecithin is utilized in the examples. The suspension is administered to an animal to treat parasitic infections. GB discloses administering the composition orally. See example A. The formulation has high antihelmithic

activity and has very high stability. Further, GB discloses that another antiparasitic in an oily suspension gives better plasma concentration of the active compound compared than the aqueous suspension. See page 1, lines 40 to page 2, line 5.

GB does not specify the type of oral administration or the instant drug.

Hauer et al teach a pharmaceutical composition containing cyclosporin, an antiparasitic, in a preconcentrate or microemulsion form. The formulation contains a hydrophilic phase, a lipophilic phase, and a surfactant. See column 6, lines 45-50 and examples. The composition may be formulated for oral administration in a unit dosage form such as hard or soft gelatin. This type of administration has the advantage of controlled release of the composition, i.e. delayed release. See column 8, lines 45-50.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of GB and Hauer et al and utilize a gelatin capsule. One would have been motivated to do so to provide the formulation in a gelatin capsule to provide for a unit dosage and to modify the release of the drug. Therefore, a skilled practitioner would utilize a capsule to provide for a unit dosage form for easier consumption and this type of dosage forms allow for one to modify the release rate. Furthermore, Hauer teaches the instant active agent. One would be motivated to utilize the instant drug to treat the desired disease.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to look to the teaching of GB and utilize an oily suspension in Hauer's formulation. One would have been motivated to do so since GB teaches the oily suspensions have better resorption of the medicament than the aqueous suspension, and give better plasma concentration.

Response to Arguments

Applicant's arguments filed 7/7/04 have been fully considered but they are not persuasive.

Applicant argues that there is not motivation to combine the references since GB only teaches niclosamide as the water-insoluble active agent. Applicant argues that GB does not disclose a self-dispersing composition in a fluid medium. Applicant argues only discloses cyclosporine. Lastly, applicant argues that GB requires the preconcentrate to be diluted in water.

With regard to the argument about the self-dispersing property, as set forth in the anticipation rejection, it is the examiner's position that GB's composition is capable of self-dispersing in an aqueous medium for the reasons set forth above. It is the applicant's burden to proves otherwise. The applicant has not done so.

Secondly, the examiner points out that GB's teachings pertain to water-insoluble active agents and it is within the skill of the art to extrapolate GB's teachings to other water-insoluble drugs such as those taught in Hauer et al.

Lastly, the applicant is incorrect that GB requires diluting the preconcentrate. GB clearly states that this is preferred on page 3, line 12 but "preferred" does not equate "required". The examiner further points out that non-preferred embodiments constitute prior art and disclosed examples and preferred embodiments do not constitute a teaching away from the broader disclosure or nonpreferred embodiments. See In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).

Therefore, the rejection is maintained.

The rejection of claims 23, 24, 39-42, and 44-54 under 35 U.S.C. 103(a) as being unpatentable over by Sato et al (5,814,324) in view of GB 1,527,638 or Brown (3,185,625) is maintained.

Sato et al teach a method of preparing injectable compositions containing the anti-fungal itraconazole. The 0.1g compound is either dispersed or dissolved in 10g of soybean oil, 10g lecithin, and 2.5g of glycerol. The fat particles have a mean size of 45 nm. See example 1 and 5 in combination.

Although Sato teaches dispersing the compound in the oil phase, the reference does not teach the particle size of the drug.

GB discloses a "preconcentrate" niclosamide suspension and method of preparing the formula. The formulation contains niclosamide (particle size of 2 to 20 microns) in sesame oil, polyoxyethylene-sorbitan monooleate, and 10% n-butanol. See examples. Additionally, lecithin is utilized in the examples. The suspension is administered to an animal to treat parasitic infections such as worms. GB discloses administering the composition orally. See example A. Lecithin is taught in example 1. GB teaches the drug particles size is usually smaller than 2 microns to prevent particle growth and thus provides good resorption of the drug. Thus, the formulation has high antihelmithic activity and has very high stability. Further, GB discloses that another antiparasitic in an oily suspension gives better plasma concentration of the active compound compared than the aqueous suspension. See page 1, lines 40 to page 2, line 5.

Brown discloses injectable substances. The drug particles of 1.5-35 millimicrons are encapsulated with a cellulose or synthetic polymers. See column 2, lines 40-61. The particle size of the encapsulated drug is small enough to pass though a hypodermic injection. See column 1,

lines 48-51. The powder are then suspended in oil (mineral oil) and emulsified with water. The surfactants taught are Tween 20, polyoxyethylene sorbitan monolaurate. See column 3, lines 5-16. Drugs taught are toxoid, antigens, anti-allergic agents, hormones, and therapeutics. See column, lines 54-60.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Sato et al and GB and utilize the instant particle size. One would have been motivated to do so since GB teaches that the instant particle size prevents particle growth and particle growth provides good resorption of the drug. Therefore, one would be motivated to use the instant size the provide for a formulation that has good resorption and stability.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Sato et al and Brown and utilize the instant particles size. One would be motivated to do so since Brown teaches the particle size of the drug, which is in the instant range, should be small enough to pass through the hypodermic needle. Therefore, it is obvious to utilize the instant particle size so that an artisan may utilize a hypodermic needle to administer the formulation if one wanted to administer the formulation via an injection.

Response to Arguments

Applicant's arguments filed 7/7/04 have been fully considered but they are not persuasive.

Applicant argues that Sato et al do not teach a self-dispersing suspension. Applicant argues that Sato et al teach an emulsifying apparatus to effect emulsification. Applicant argues that there is not motivation to combine the references since GB only teaches niclosamide as the

water-insoluble active agent. Applicant argues that GB does not disclose a self-dispersing composition in a fluid medium. Lastly, applicant argues that GB requires the preconcentrate to be diluted in water. Applicant argues that Brown teach a particle range of 1.5 to 35 milllimicrons whereas instant application' claims 0.1 to 10 micrometers. Applicant argues that Brown does not teach a self-dispersing composition.

Firstly, it is pointed out that the limitation "wherein upon addition of said composition..." is intended use since the claim does not *require* the addition of the fluid aqueous medium. It is the examiner's position that Sato's composition is inherently capable of self-dispersing and the rationale is as follows. Firstly, the instant composition and Sato et al are not patentably distinct in structure. Therefore, if the instant claim is capable of dispersing in an aqueous medium, then the prior art must also inherently be capable since both composition are the same. Secondly, it is well known that oil and water are not miscible and thus applicant's argument refuting this is perplexing. Therefore, an oil suspension will inherently disperse when contacted with an aqueous medium.

Moreover, the examiner points to example 1 wherein Sato et al actually teaches adding an aqueous medium to the oil suspension which disperses to yield an emulsion with fat particle (which contains the drug particles) have a mean particle size of 764 nm (.7 micrometers). An emulsion is defined as a two-phase system wherein the two phases are immiscible. Therefore, Sato et al teach the preconcentrate is capable of self-dispersing.

The merits of Brown and GB have been addressed above. The examiner points out that GB and Brown are solely relied upon for the active particle size. GB teaches the instant particle size to provide good resorption and Brown teaches the instant drug particle size is small enough

to pass through the hypodermic needle. Therefore, ample motivation is provided by the secondary references to utilize the instant particle size in Sato's composition.

Therefore, the rejection is maintained.

Conclusion

None of the claims are allowed at this time.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sharmila S. Gollamudi
Examiner
Art Unit 1616

SSG

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